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Original Article

COVID-19 IN PATIENTS WITH BEHCET'S DISEASE: OUTCOMES AND RATE OF BEHÇET'S EXACERBATIONS IN A RETROSPECTIVE COHORT

Running Title: COVID-19 IN BEHÇET'S DISEASE

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ABSTRACT

Objectives: Aim of this study is to investigate the outcomes of coronavirus disease 2019 (COVID-19) in our cohort of Behçet's disease (BD) patients in means of mortality, admission to hospital and/or intensive care unit and length of hospital stay, additionally, to reveal rate of BD exacerbations due to COVID-19.

Methods: A retrospective cohort was formed from patients who have previously been followed with a diagnosis of BD. Patients of this cohort were retrospectively evaluated for a positive severe acute respiratory syndrome – coronavirus 2 (SARS-CoV 2) polymerized chain reaction (PCR) test result. In PCR positive patients, demographics, comorbid diseases, active medical treatment for BD and information regarding hospitalization, intensive care unit admission, mortality were collected from medical records. PCR positive patients were reached via phone numbers and *Behçet's Disease Current Activity Form* (BDCAF) scores for pre and post-COVID-19 BD symptoms were calculated.

Results: Out of a total 648 BD patients, 59 were detected to have a positive SARS-CoV 2 PCR test. 88.1% of these patients were under colchicine treatment and 28.8% of patients were under azathioprine treatment. 3 of the 59 patients (5.0%) were found to be hospitalized, none of them was admitted to the intensive care unit or died. An increasing trend in the frequency of comorbid diseases and older age was observed in hospitalized patients. 32.2% of BD patients suffered from exacerbation of at least one symptom related to BD when evaluated with BDCAF, arthralgia/arthritis being the most common.

Conclusions: We observed no intensive care unit admission or mortality with COVID-19 in our BD patient cohort. A substantial number of patients suffered from exacerbation of BD symptoms.

INTRODUCTION

Pandemic of coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome – coronavirus 2 (SARS-CoV 2), has become a major global health issue since December 2019. Although most patients suffer mildly, a considerable number of patients, particularly with older age and comorbidities, have a severe disease with increased risk of mortality and morbidity [1]. Initial symptoms of COVID-19 usually resembles an upper respiratory tract infection and in some cases, progress to pneumonia, acute respiratory distress syndrome (ARDS), and multi-organ failure [2]. Moreover, complications due to thrombotic events have also frequently been observed in the course of COVID-19 [3].

Behçet's disease (BD) is a systemic vasculitic condition, in which all types of vessels in circulatory system may be involved, with increased prevalence particularly in Mediterranean and Far East regions along the

"Old Silk Road". Venous thrombosis is a characteristic involvement in BD. Furthermore, colchicine is frequently used in BD patients along with other immunosupressive and anti-inflammatory agents. Since thrombotic events are also frequent in COVID-19 and colchicine treatment had promising results in several studies, it is intriguing whether these intersections of both conditions have an effect on COVID-19 outcomes. Although there are studies investigating the course of COVID-19 in various rheumatologic disorders, knowledge about COVID-19 outcomes in BD is scarce. There are two case series, to our best knowledge, evaluating patients with BD who had COVID-19. In a study conducted in Spain, among 2135 patients with COVID-19 only four patients had BD with comparable outcomes to the normal population [4]. In the other study conducted in Turkey, 767 patients with COVID-19 were analyzed and only ten patients with BD were detected. It was reported that despite BD patients were younger, rate of severe COVID-19 was observed to be increased, therefore cautious monitoring of BD patients with COVID-19 was recommended [5].

As a clinic from the country with highest BD prevalence, here in this study, we aimed to further contribute to the current knowledge about COVID-19 course in BD patients by retrospectively investigating our BD cohort. Furthermore, we also evaluated the rates of BD exacerbations and discontinuation of BD treatment during COVID-19.

METHOD

We retrospectively evaluated the BD patients followed in our clinic using hospital records and formed a retrospective cohort from patients who meet *International Study Group* (ISG) criteria [6]. Between January 1 and 15, 2021, patients of this cohort were retrospectively investigated for a recorded SARS-CoV 2 polymerized chain reaction (PCR) test result from a nasopharyngeal swab between March 11 and January 01, 2021 by using Public Health Management System (HSYS), to which all cases with a PCR test were registered during the pandemic in our country. Patients with a positive PCR result were enrolled in the study. Patients younger than 18 years of age and who were pregnant during COVID-19 infection were excluded. The study was conducted with approval by our institutional ethics committee and was therefore performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. An official permission was also obtained from Ministry of Health.

Patient demographics, comorbid diseases and active BD treatments were collected from our hospital records. Rates of hospitalization, intensive care unit (ICU) admission and mortality due to COVID-19 were selected as main outcome variables and collected from medical records and HSYS. Thereafter, all patients were

reached by phone via the phone numbers recorded in our hospital database. Upon verbal consent, patients were questioned for COVID-19 symptoms during disease period, continuation to BD treatment and BD symptoms before and after COVID-19. BD symptoms were evaluated using the Turkish version of the *Behçet's Disease Current Activity Form* (BDCAF) [7]. BDCAF scores the presence of symptoms in 12 clinical categories over the four weeks prior to the day of assessment. Clinical symptoms include headache, oral ulcers, genital ulcers, erythema nodosum, skin pustules, arthralgia, arthritis, nausea or vomiting or abdominal pain, diarrhea or hematochezia, and symptoms related with eye, nervous system, and major vessels involvement. BDCAF was fulfilled for both pre-COVID-19 and post COVID-19 BD symptoms. If any new complaint was defined by the patient in the post-COVID-19 questionnaire, we considered that as a BD exacerbation. In post-COVID-19 assessment, presence of a symptom was accepted meaningful for BD, if it was present at least one month after the COVID-19 infection period. All data were collected using a standardized case-report form by the same physician (BP).

Data were analyzed using Statistical Package for the Social Sciences (SPSS) 22.0 software. Shapiro-Wilk's test was used to determine the distribution of the data. The distribution of continuous data was expressed as mean ± standard deviation. Continuous variables that did not conform to normal distribution were expressed as median and minimum-maximum values. Continuous variables were compared by using either student t-test or Mann-Whitney-U test according to normality. For comparison of categorical variables x^2 test was used and the outcomes were expressed as number and percentages. P values below 0.05 were considered statistically significant.

RESULTS

Our cohort consisted of a total 648 BD patients. Among these, 59 (9.1%) patients were detected to have a positive SARS-CoV-2 PCR test. 3 of the 59 patients (5.0%) were found to be hospitalized for COVID-19 infection and none of them were admitted to ICU or died (Table 1). All three patients had pneumonia according to thorax computed tomography reports in medical records. The median length of hospital stay was found to be five days. Demographic features, comorbidities, and medical treatments for BD of these patients were given in Table 1. The percentages of patients under colchicine treatment and azathioprine treatment were 88.1% and 28.8%, respectively (Table 1).

All 59 patients with a positive PCR were reached via phone and accepted enrollment. The number of patients who interrupted and/or discontinued BD treatment after the diagnosis of COVID-19 was 10 (16.9%).

Distribution of the treatment agents in patients who interrupted and/or discontinued their treatment was as follows: 5 (50.0%) azathioprine, 4 (40.0%) colchicine, and 1 (10.0%) methotrexate.

In PCR positive patients, the pre-COVID-19 median (IQR) BDCAF score was 2 (3), while post-COVID-19 score was 3 (2) ($p < 0.001$). 19 (32.2%) patients had an exacerbation of a BD related symptom after COVID-19 (Figure 1). Most common symptoms were oral ulcers in 12 (63.1%) patients and arthralgia/arthritis in ten patients (52.6%). In patients with arthralgia/arthritis, affected joints were knees in 9 (90%), ankles in 9 (90%), wrists in 6 (60%), elbows in 3 (30%), shoulders in 1 (10%) and hand joints in 1 (10%). 5 (50%) had polyarticular, 4 (40%) had oligoarticular and 1 (10%) had monoarticular involvement (ankle). 2 patients had arthritis and ankle was the affected joint in both. None of the patients reported inflammatory axial pain, yet 4 (40%) had non-specific back and gluteal pain. Deep vein thrombosis developed in one (5.2%) patient while receiving COVID-19 treatment. On the other hand, deep vein thrombosis developed in another (5.2%) patient approximately one month after COVID-19 treatment. Out of the 19 patients with exacerbations, 8 had combined clinical manifestations (5 (26.3%) oral ulcer and arthralgia/arthritis, 1 (5.3%) oral and genital ulcers, 1 (5.3%) oral ulcer and skin lesions, 1 (5.3%) oral and genital ulcers and arthralgia/arthritis). BD exacerbation was observed in 4 (21.1%) patients who discontinued BD treatment, while 6 (15%) patients who continued BD treatment had an exacerbation ($p = 0.563$) (Figure 1 and Table 2).

There was no difference in terms of age, gender, and comorbidity between patients with and without exacerbations (Table 2). When COVID-19 symptoms were compared, dyspnea, headache and arthralgia were more common in the exacerbation group (13 (68.4%) vs 12 (30%), $p=0.005$; 13 (68.4%) vs 15 (37.5%), $p=0.02$; 17 (89.5%) vs 11 (27.5%), $p<0.001$, respectively).

When BD patients were grouped according to involved organ systems prior to COVID-19 infection, 31 of 59 (52.6%) BD patients had mucocutaneous involvement and 28 (47.4%) patients had at least one organ involvement (vascular, neurological, ocular). Two of the hospitalized patients (6.5%) were in the mucocutaneous group. While 9 (29%) of the patients with BD exacerbation were in the mucocutaneous group, 10 (35.7%) were in the organ involvement group ($p = 0.583$) (Table 3). In 12 out of 59 patients human leukocyte antigen (HLA) type had been tested and 10 of them were positive for HLA-B51. One of the outpatients with COVID-19 had a diagnosis of lymphoma and was followed by hematology in remission for two years.

DISCUSSION

Our results demonstrated that among 59 BD patients with a positive SARS-CoV-2 PCR, 5.1% were hospitalized and none were admitted to ICU or died. 32.2% of BD patients suffered from exacerbation of at least one symptom related to BD when evaluated with BDCAF with arthralgia/arthritis being the most common. Median age and comorbid conditions seemed to be increased in hospitalized patients. Type of BD involvement (mucocutaneous vs organ involvement) was not associated with COVID-19 severity or BD exacerbation after COVID-19 infection. Furthermore, discontinuation to BD treatment during COVID-19 infection was not significantly related with BD exacerbation.

In Hong Kong records, among 39,835 patients with a rheumatologic condition 0.126% had COVID-19, while incidence was 0.142% in the normal population. It was reported that the incidence of COVID-19 was lower in patients with a rheumatologic condition [8]. A total of 4820 COVID-19 cases were registered in the *Global Rheumatology Alliance* (GRA) records as of January 5, 2021. 39.6% (1908) of these patients were diagnosed with rheumatoid arthritis, 18.26% (880) with systemic lupus erythematosus, 8.1% (391) with psoriatic arthritis, and 6.95% (335) with spondylitis [9]. In *European League Against Rheumatism* (EULAR) registry report of February 2021, 1 % of rheumatism patients with COVID-19 were BD patients [10].

It is well known that age, gender, and comorbidities are associated with worse outcomes in COVID-19 [11]. Fredi et al. [12] demonstrated that in patients with rheumatic conditions, worse outcomes were associated with older age and comorbidities rather than the type of rheumatologic condition and the degree of immunosuppression. In our study, two of the hospitalized patients had comorbidities, one had asthma and the other one had hypertension.

There is scarce data about the course of COVID-19 in BD. In the study of Espinosa et al. [4] 3 (75%) of the BD patients with COVID-19 had mild disease with upper respiratory tract symptoms, 1 (25%) had pneumonia and none of the patients required intensive care or mechanical ventilation. Yurttaş et al. [5] revealed that pneumonia was detected in 6 (60%) of 10 BD patients with COVID-19 and 1 (10%) patient needed intensive care. In our study, all 3 of the hospitalized patients had pneumonia and none of the patients required mechanical ventilation or intensive care.

No death due to COVID-19 was observed in our cohort. In the study conducted by Baloch et al. [13], the death and recovery rates of patients diagnosed with COVID-19 from 197 different countries were investigated. Among 411,179 patients, mortality was observed in 18,444 (4.4%) patients while 113,822 (27.5%) patients were recovered and discharged. In the data published by the World Health Organization on February 22, 2021, it was determined that there were 111,102,016 confirmed cases and 2,462,911 (2.2%) deaths worldwide

[14]. In a meta-analysis involving 1994 patients, the discharge rate of the patients was 52% and the mortality rate was 5% [15]. In a study conducted in Wuhan, 2326 patients diagnosed with COVID-19 were analyzed and 21 of them had rheumatologic conditions. Hospitalization and mortality rates were similar between patients with and without rheumatologic conditions [16]. In GRA registry, COVID-19 related death was observed in 390 (10.5%) of 3729 rheumatism patients between March 24 and July 1, 2020 [17]. According to the registry of Health Ministry as of January 1, 2021, number of confirmed COVID-19 cases was 2,220,855 (approximately 2.7 % of the general population) with 21,093 deaths (0.99 %) in general population of our country [18]. Although our sample size was small, lack of mortality is still noteworthy which may be due to the fact that the average age of the patients lower and /or most of the patients use colchicine.

Colchicine is a mainstay drug in BD due to anti-inflammatory effects and is also thought to reduce thrombotic events [19,20]. Colchicine inhibits the migration of neutrophils to the inflammatory site, Nod-like receptor protein 3 (NLRP3) inflammasome formation and microtubule polymerization [19,20]. Accordingly, colchicine has been discussed as a treatment option in COVID-19 [21]. In COLCORONA study, among non-hospitalized COVID-19 patients, lower rate of hospitalizations or deaths were observed with colchicine when compared to placebo (4.7% vs 6%, $p < 0.04$) [22]. The majority of patients in our study were under colchicine and this may be related to relatively low number of hospitalizations and absence of cytokine storm in any patient, however our results are not sufficient enough for precise conclusions about effects of colchicine.

In 21 patients with rheumatic conditions, Ye et al. [16] reported that common COVID-19 symptoms were fever (76%), malaise (43%) and diarrhea (23%). In the study of Espinosa et al [4], headache was present as a COVID-19 symptom in 3 (75%) BD patients, while dyspnea and arthralgia were not observed. In the study of Yurttaş et al. [5] headache and arthralgia were seen in 2 patients, and dyspnea was not observed in any patient. The most common COVID-19 symptoms seen in our study were fever and myalgia. 28 (47%) of 59 patients had a headache, 25 (42%) had dyspnea, and 28 (47%) had arthralgia.

Both BD and COVID-19 increase the risk of thrombosis [19,23]. However, thrombosis was not observed in any of the patients in the study of Espinosa et al. [4] and *de novo* thrombosis was detected in one patient in the study of Yurttaş et al. [5]. In our study, thrombosis developed in two (3.4%) patients, both of which had prior history of deep vein thrombosis. However, it is not possible to distinguish whether the newly developed thrombosis is a complication of COVID-19 or BD exacerbation in our study setting.

Ye et al. [16] reported an exacerbation of the underlying rheumatologic condition was observed in 4 of 21 rheumatism patients during COVID-19 infection. In this study, attention was drawn to the difficulty of

differentiating whether a symptom is an exacerbation of a rheumatic condition or related to COVID-19 infection. Espinosa et al. [4] observed BD exacerbation (oral ulcers and erythema nodosum) in one patient while receiving COVID-19 treatment and another one experienced an exacerbation 15 days after COVID-19 (oral aphthae and genital ulcer). Exacerbations of both cases were improved with colchicine. In the study of Yurttas et al. [5], 2 (20%) patients had oral ulcers and 1 (10%) patient had arthralgia as *de novo* symptoms related to BD activation. In our study, *de novo* BD symptoms after at least one month from COVID infection were observed in 19 (32.2%) patients. 12 (63.1%) had oral ulcers, 10 (52.6%) had arthritis/arthralgia and less frequently genital ulcer, thrombosis, skin lesions were observed (Figure 1). 4 (21.1%) of 19 patients with an exacerbation had discontinued BD treatment.

BDCAF scores of 4 patients in the study of Espinosa et al. [4] were calculated when they had the first COVID-19 symptom, and all BDCAF scores were found to be below 3. In our study we evaluated and compared BDCAF scores before and at least one month after COVID-19 infection. There was a significant increase in median (IQR) BDCAF scores after COVID-19 (2 (3) vs 3 (2), $p<0.001$), possibly suggesting an overall increase in BD symptoms with COVID-19.

The retrospective nature of the study and the small sample size were the major limitations of our study. Nevertheless, to our best knowledge, this is the study with highest number of SARS-Cov-2 PCR positive BD patients. Another major limitation is the fact that it is quite difficult to differentiate whether some symptoms like arthralgia and thrombosis were related to BD exacerbation or COVID-19. In order to avoid this conflict as much as we can, we evaluated post-COVID-19 BDCAF after at least one month from COVID-19 infection period. However, since some COVID-19 patients are known to suffer from prolonged symptoms, this issue remained controversial. Lastly, BDCAF questionnaire was completed via phone calls in BD patients which may have caused over or under estimation of BDCAF scores since physical examination lacked.

To conclude, in our cohort, we observed no ICU admission or mortality with COVID-19 in BD patients, which may be related to colchicine use or relatively younger age of our patients. A substantial number of patients suffered from exacerbation of BD symptoms. Further studies will contribute to better elucidate the COVID-19 course in BD.

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CONFLICTS OF INTEREST

None

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FIGURE LEGENDS

Figure 1. Aggravated symptoms in BD patients during COVID-19

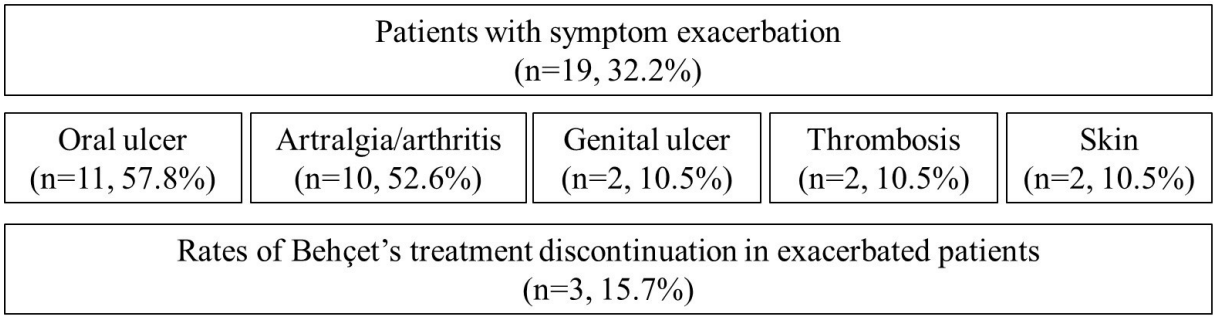

Table 1. Demographic and clinical characteristics of the patients at baseline

	All (n=59)	Hospitalized (n=3)
Age, years, median (min-max)	40 (20-67)	52 (26-53)
Gender, male, number (%)	37 (62.7)	1 (33.3)
Patients with ≥1 comorbidities, number (%)	24 (40.7)	2 (66.6)
Active smokers, number (%)	18 (30.5)	1 (33.3)
Comorbidities, number (%)		
Hypertension	13 (22)	1 (33.3)
Diabetes	4 (6.8)	0 (0)
Malignancy	1 (1.7)	0 (0)
Asthma or COPD	5 (8.5)	1 (33.3)
Coronary artery disease	2 (3.4)	0 (0)
Active medical treatment for BD, number (%)		
Colchicine	52 (88.1)	3 (100)
Azathioprine	17 (28.8)	0 (0)
Cyclosporine	1 (1.7)	0 (0)
TNFa inhibitors	2 (3.4)	0 (0)
COVID-19 course		
Need to oxygen supplement, number (%)	2 (3.4)	
Hospitalization, number (%)	3 (5.0)	
Length of hospital stay (days), median (min-max)	5 (4-9)	
ICU admission, number (%)	0 (0)	
Death, number (%)	0 (0)	

COVID-19: coronavirus disease 2019, PCR: polymerized chain reaction, n: number, min-max: minimum-maximum, TNFa: tumor necrosis factor alpha, ICU: intensive care unit, COPD; Chronic obstructive pulmonary disease. BD: Behcet's Disease.

Table 2. Comparison of COVID-19 symptoms and characteristics of BD patients who had COVID-19 with or without exacerbation during follow-up

	BD exacerbation group (n=19)	BD non-exacerbation group (n=40)	p
Male sex, n (%)	11 (57.9)	26 (65)	0.598
Age (years), median (min-max)	37 (27-57)	40.5 (20-67)	0.516
COVID-19 symptoms on admission, n (%)			
Cough	12 (63.2)	17 (42.5)	0.138
Fever	11 (57.9)	23 (57.5)	0.977
Dyspnea	13 (68.4)	12 (30)	**0.005**
Headache	13 (68.4)	15 (37.5)	**0.02**
Arthralgia	17 (89.5)	11 (27.5)	**<0.001**
Myalgia	8 (42.1)	26 (65)	0.096
Anosmia	7 (36.8)	10 (25)	0.348
Ageusia	8 (42.1)	13 (32.5)	0.472
Abdominal Pain	2 (10.5)	0 (0)	0.1
Patients with ≥1 comorbidities, n (%)	8 (42.1)	16 (40)	0.878
Patient discontinued medication, n (%)	4 (21.1)	6 (15)	0.563

*BD: Behçet's disease, COVID-19: coronavirus disease 2019, n: number, min: minimum, max: maximum, * p<0.05.*

Table 3. Comparison of COVID-19 outcomes and rates of BD exacerbations between BD patients with mucocutaneous involvement alone and with organ involvement

	BD with mucocutaneous involvement (n=31)	BD with organ involvement (n=28)	p
Need to oxygen supplement, n (%)	2 (6.5)	0 (0)	0.493
Hospitalization, n (%)	2 (6.5)	1 (3.6)	1
BD with exacerbation, n (%)	9 (29)	10 (35.7)	0.583

BD: Behçet's disease, n: number